IN THE UNITED STATES PATENT AND TRADEMARK EXAMINER

Application of:	Ravikumar et al.	Confirmation No.:	4970
Serial No.:	10/510,667	Art Unit:	1635
Filed:	April 5, 2005	Examiner:	Vivlemore, Tracy Ann
For:	OLIGOMERIC COMPOUNDS HAVING MODIFIED PHOSPHATE GROUPS	ISIS Ref:	ISIS-5582

BRIEF ON APPEAL

Mail Stop Appeal Brief - Patents

Commissioner for Patents

P.O. Box 1450

Alexandria, VA 22313-1450

Sir:

Pursuant to the provisions of 35 U.S.C. §134 and 37 C.F.R. 41.37, an appeal is taken herein from the final rejection dated November 25, 2008.

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I. REAL PARTY IN INTEREST

The real party in interest is Isis Pharmaceuticals, Inc., the assignee of record of the above-identified application.

II. RELATED APPEALS AND INTERFERENCES

Appellants and their legal representatives respectfully submit that they are not aware of any appeals, interferences, or judicial proceedings that may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

III. STATUS OF CLAIMS

Claims 2, 3, 5-10 and 24-41 are canceled

Claims 19 and 21-23 are withdrawn.

Claims 1, 4, 11 to 18 and 20 are under final rejection

Claims 1, 4, 11 to 18 and 20 are pending.

Claims 1, 4, 11 to 18 and 20 are pending and under final rejection. These claims are the subject of this appeal.

IV. STATUS OF AMENDMENTS

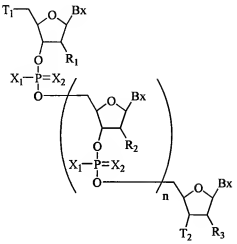
No amendments were filed after the final Office Action mailed November 25, 2008. Accordingly, the claims on appeal are those submitted in the response filed with a Request for Continued Examination on February 25, 2008, which were entered and examined in subsequent actions including the final Office Action mailed November 25, 2008. A listing of the claims on appeal is presented in the **CLAIMS APPENDIX** of this paper.

V. SUMMARY OF CLAIMED SUBJECT MATTER

Claims 1, 4, 11 to 18 and 20 recite, *inter alia*, oligomeric compounds comprising a 5'-phosphate moiety.

An explanation of the subject matter defined in each independent claim is provided below. MPEP §1205.02.

Claim 1 recites, *inter alia*, an oligomeric compound having the formula:



wherein:

each Bx is, independently, a heterocyclic base moiety;

T_2 is hydroxyl, or a protected hydroxyl;

T_1 is a modified phosphate having the formula:

wherein

Q is OH or CH_3

R_1, R_3 and each R_2 are, independently, hydrogen, hydroxyl, a sugar substituent group or a protected sugar substituent group;

each X_1 and X_2 is, independently, O or S wherein at least one X_1 is S; and

n is from 3 to 48.

See, e.g., Specification, pages 7 to 9, paragraph 24; pages 10 to 11, paragraph 28 and 29; page 23, paragraph 59; and pages 58-63, Examples 16 to 21;

Claim 20 recites, *inter alia*, a composition comprising:

a pharmaceutically effective amount of an oligomeric compound of claim 1; and

a pharmaceutically acceptable diluent or carrier.

See, e.g., Specification, page 30, paragraph 78.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The issue presented to the Board is whether each of the present claims, 1, 4, 11 to 18 and 20, is rendered obvious under 35 U.S.C. § 103(a) by U.S. patent number 6,033,909 to

Uhlmann et al., in view of the combined teachings of Kostenko et al., Nucleic Acids Research 2001, 29(17), 3611-3620 ; Hamma et al., Biochemistry, 1999, 38, 15333-15342; and Sproat et al., Nucleic Acids Research, 1987, 15(12), 4837-4848.

VII. ARGUMENT

A. The Examiner has improperly rejected claims 1, 4, 11 to 18 and 20 as allegedly rendered obvious under 35 U.S.C. § 103(a)

The Examiner has improperly rejected claims 1, 4, 11 to 18 and 20 as allegedly rendered obvious under 35 U.S.C. § 103(a) over U.S. patent number 6,033,909 to Uhlmann et al., (Uhlmann) in view of the combined teachings of Kostenko et al., Nucleic Acids Research 2001, 29(17), 3611-3620 (Kostenko); Hamma et al., Biochemistry, 1999, 38, 15333-15342 (Hamma); and Sproat et al., Nucleic Acids Research, 1987, 15(12), 4837-4848 (Sproat). The rejection is set forth in the Office Action dated May 14, 2008 ("Office Action"), page 4; and the Final Action dated November 25, 2008 ("Final Action"), page 2. The Examiner argues that "it would have been obvious to one of ordinary skill in the art at the time the invention was made to produce oligonucleotides comprising 5' mercapto nucleotides and a 5' phosphate as taught by Uhlmann et al., and to make such an oligonucleotide comprising a 3' hydroxyl". The Examiner further argues that "based on the teaching of Sproat et al., of 5' mercapto nucleoside phosphoramidites suitable for incorporation at any point in a synthetic oligonucleotide, one of ordinary skill in the art would recognize the use of this particular monomer to be a matter of simple substitution of known equivalents that would predictably provide 5' mercapto oligonucleotides." The Examiner also asserts that "based on the teachings of Kostenko et al., and Hamma et al., "one of ordinary skill in the art recognizes that synthesis of 5' phosphate oligonucleotides is routine in the art, therefore the synthesis of oligonucleotides comprising both a 5' mercapto nucleotide and a 5' phosphate is a matter of design choice made in the course of routine optimization using equivalent elements known to those of ordinary skill in the art" (Final Action starting at page 4).

However, as set forth below, the Examiner's rationale fails to establish a *prima facie* case of obviousness under the current post-*KSR* standard of obviousness. Specifically, the Examiner fails to establish (1) that a person skilled in the art would have had a reason to

actually select the oligonucleotides of Uhlmann for further investigation and (2) even assuming one skilled in the art would have started with the oligonucleotides of Uhlmann why a person skilled in the art would have had a legally sufficient reason to perform each of the specific modifications required to arrive at the instantly claimed oligomeric compounds.

1. Post-*KSR* standard of obviousness for new chemical compounds – two step lead compound analysis

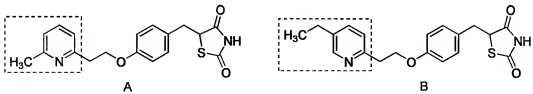
"The determination of obviousness is a matter of law based on findings of underlying fact, wherein the factors identified in *Graham v. John Deere Co*...guide the inquiry...." *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1085, 89 USPQ2d 1370, 1377 (Fed. Cir 2008), citing *Graham v. John Deere Co.*, 383 U.S. 1, 86 S.Ct. 684, 15 L.Ed.2d 545, 148 USPQ 459 (1966). The Supreme Court recently emphasized that the proper inquiry for obviousness determinations focuses on the factors identified in *Graham*. *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 127 S.Ct. 1727, 82 USPQ2d 1385 (2007) The factors identified in *Graham* are: (1) "the scope and content of the prior art;" (2) "the differences between the prior art and the claims;" (3) "the level of ordinary skill in the pertinent art;" and (4) "secondary considerations." *Graham*, 383 U.S. at 17-18, 148 USPQ at 467. In determinations of obviousness, "[a] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR*, 127 S.Ct. at 1741, 82 USPQ2d at 1396.

After *KSR*, the Federal Circuit decided three cases that together embody the current standard of obviousness for new chemical compounds: *Takeda*, *Eisai*, and *Proctor & Gamble*. *Proctor & Gamble*, 2009 WL 1313321 (Fed. Cir. May 13, 2009); *Eisai Co., Ltd. v. Dr. Reddy's Laboratories, Ltd.*, 533 F.3d 1353, 87 USPQ2d 1452 (Fed. Cir. 2008); *Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 83 USPQ2d 1169 (Fed. Cir. 2007), *cert denied*, 128 S. Ct. 1739 (2008). These three cases show that structural similarity alone is not a proper basis for establishing a ***prima facie*** case of obviousness. *Proctor & Gamble*, 2009 WL 1313321; *Eisai*, 533 F.3d at 1359, 87 USPQ2d at 1457; *Takeda*, 492 F.3d at 1357, 83 USPQ2d at 1174. In all three of these cases, a two-step analysis was applied. *Proctor & Gamble*, 2009 WL 1313321; *Eisai*, 533 F.3d at 1359, 87 USPQ2d at 1457; *Takeda*, 192 F.3d at 1356, 83 USPQ2d at 1179.

First a determination was made as to whether one skilled in the art would have had a reason to select a lead compound as a starting point for further study. *See, e.g., Eisai,* 533 F.3d at 1359, 87 USPQ2d at 1457 ("post-*KSR*, a *prima facie* case of obviousness for a chemical compound still, in general, begins with the reasoned identification of a lead compound.").

Second, a determination is made as to whether one skilled in the art would have had a reason to modify the lead compound to arrive at the claimed compound. *See, e.g., Takeda,* 492 F.3d at 1357, 83 USPQ2d at 1174 ("in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish *prima facie* obviousness of a new claimed compound.").

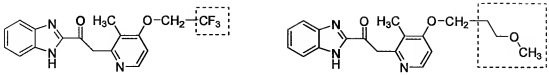
Following the analysis above, the Federal Circuit in *Takeda* found that (1) a person skilled in the art would not have had a reason to select compound A (Figure 4) as a lead compound; and (2) a person skilled in the art would not have had a reason to modify compound A to arrive at the claimed compound B (Figure 1). 492 F.3d at 1356-1363, 83 USPQ2d at 1174-1179.



Takeda
B held not obvious over A

Figure 1

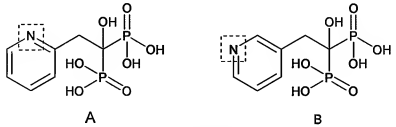
Similarly, the Federal Circuit in *Eisai* found that even assuming that one skilled in the art had a reason to select compound A (Figure 2) as a lead compound, the record did not support a finding of obviousness because it contained no reason why a person skilled in the art would have considered the required modifications to arrive at compound B (Figure 5). 533 F.3d at 1359, 87 USPQ2d at 1457.



Eisai
B held not obvious over A

Figure 2

Similarly, the Federal Circuit in Proctor & Gamble found that even assuming that one skilled in the art had a reason to select compound A (Figure 3) as a lead compound, compound B was not obvious because the patent challenger established "insufficient motivation" for a person of ordinary skill in the art to make the required modifications. *Proctor & Gamble*, 2009 WL 1313321.



Proctor & Gamble
B held not obvious over A

Figure 3

Applying the two-step analysis of *Takeda* and *Eisai* to the instant case, the Examiner has not established a *prima facie* case of obviousness because (1) a person skilled in the art would not have had a reason to select the compounds of Uhlmann as a starting point for further study and (2) even if the compounds of Uhlmann were selected for further study, a person skilled in the art would not have had a reason to modify the compounds of Uhlmann to arrive at the instant oligomeric compounds.

2. The Examiner fails to establish why one would have had a reason to select the compounds of Uhlmann for further study

The Examiner relies heavily on Uhlmann for its determination of obviousness, but fails to meet its burden in establishing why a person of ordinary skill in the art would have even started with Uhlmann and selected the compounds disclosed therein for further study. As discussed above, the Federal Circuit has emphasized that establishing the obviousness of new chemical compounds, after KSR, "clearly depends on a preliminary finding that one of ordinary skill in the art would have selected the prior art compound as a lead compound." Proctor & Gamble, 2009 WL 1313321 (citing Takeda, 492 F.2d at 1359, 83 USPQ2d at 1174); see also, Eisai, 533 F.3d at 1359, 87 USPQ2d at 1457 ("[P]ost-KSR, a prima facie case of obviousness for a chemical compound still, in general, begins with the reasoned identification of a lead compound."). The Examiner has failed to establish such a preliminary finding and thus, the rejection under 35 U.S.C. §103 is improper.

Uhlmann discloses a broad genus encompassing a vast number of possible compounds of formula I. However, the Examiner has not explained why a person skilled in the art seeking to develop antisense compounds would have had a reason to specifically focus on the compounds of Uhlmann. In order to provide the compounds instantly claimed one would have to select a particular subgenus of the compounds of Uhlmann and then modify the subgenus in a manner that would be contrary to the teachings in the disclosure. This is important in view of *Takeda*, where the Federal Circuit found the compounds at issue non-obvious because one of ordinary skill in the art would not have selected a particular prior art compound as a starting point in view of a prior art disclosure of "a broad selection of compounds any one of which could have been selected as a lead compound for further investigation." 492 F.3d at 1359, 83 USPQ2d at 1176. Similar to *Takeda*, there was a broad selection of oligomeric compounds available to those skilled in the art at the time of the invention, including those disclosed in Uhlmann, any one of which could have been selected as a candidate for further investigation as, for example, an antisense compound. Since there was a broad selection of possibilities in the art, the Examiner is required to show why a person skilled in the art would have had a reason to specifically single out the compounds of Uhlmann for further study. The Examiner has not done so. Absent a reason to single out the compounds disclosed in Uhlmann from the broad selection of other known candidates, the selection of the compounds of Uhlmann at the time of the invention could not have been obvious. It is, therefore, only through hindsight analysis and "reverse engineering" – which

have no place in a proper obviousness determination – that one could be able to single out the compounds of Uhlmann as a starting point.

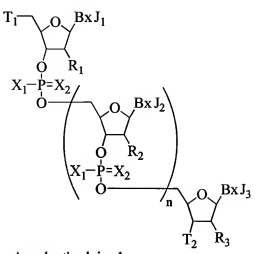
In sum, the Examiner has failed to show why a person skilled in the art would have had a reason to select the compounds of Uhlmann as a starting point for further study, and thus fails to establish a *prima facie* case of obviousness. This alone is sufficient to render the Examiner's rejection improper. *See, e.g., Eisai,* 533 F.3d 1353, 87 USPQ2d at 1457 ("post-*KSR*, a *prima facie* case of obviousness for a chemical compound still, in general, begins with the reasoned identification of a lead compound.").

3. The Office fails to establish why a person skilled in the art would have had a reason to select each of the required Markush variables of Uhlmann and then further modify the resulting compound to arrive at the instantly claimed compounds

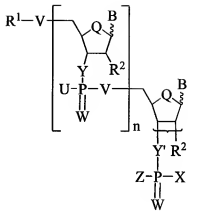
Even assuming, *arguendo*, that a person skilled in the art would have decided to select the compounds of Uhlmann for further study, the Examiner has not provided a reason why a person skilled in the art would have made each required modification to arrive at the claimed compounds. Uhlmann did not provide a reason to pursue to the required modifications. Kostenko, Hamma and Sproat do not cure this defect of Uhlmann or provide the requisite evidence that one of ordinary skill in the art would have reasonably expected success with the claimed compounds.

a. <u>The required modifications</u>

As reproduced below, Uhlmann teaches a large genus of oligomeric compounds having formula I. To arrive at the instantly claimed oligomeric compounds from the compounds of Uhlmann, at least 7 variables need to be specified in addition to removing the 5'-phosphoryl group which is the main focus of Uhlmann's invention.



Appelant's claim 1



formula I (Uhlmann)

Figure 4

The Examiner asserts that "to provide a 5' thiophosphate from Formula I, one of ordinary skill in the art would have to choose only two variables, R^1 and V" Final Action at page 5. However, as can be seen in formula I above in Figure 4, the selection of R^1 and V only provides another genus of oligonucleotides wherein the instantly claimed oligomeric compounds would then be a species only if further modified. To provide the instantly claimed oligomeric compounds at least 7 variables would have to be specified and then the phosphoryl group would have to be removed from the 3' position. One skilled in the art would have to select the following variables in the compounds of Uhlmann:

R^1: a radical of the formula II (still doesn't include each embodiment of the instant claims);

V: V thio (5'-terminal), remaining Vs (as per the value of n) oxo;

Q: oxo (not defined in columns 3 or 4)

Y: oxo;

U: hydroxy or mercapto; and

W: oxo or thioxo.

The Examiner has not established why a person of ordinary skill in the art would have had a reason to carry out any of the required modifications. The prevailing case law requires this for establishing the obviousness of new chemical compounds. *See e.g. Takeda*, 492 F.2d at 1360-1361, 83 USPQ2d at 1177 (holding new compound non-obvious in part because

patent challenger did not establish why one would have had a reason to perform each required modification step, *i.e.*, "ring walking" and "homologation"); *see, also Abbott*, 544 F.3d at 1351, 89 USPQ2d at 1170-1171 (applying principle that proper obviousness determination requires the consideration of each and every claim limitation). The required modifications, when taken individually, are not obvious over Uhlmann. The claims are even less obvious when all the limitations are considered together, *i.e.*, the claimed invention is considered as a whole. Kostenko, Hamma and Sproat do not cure this defect of Uhlmann.

b. Uhlmann would not have provided a reason to perform any of the required modifications

The teachings of Uhlmann would not have provided a reason to pursue any of the required modifications, much less the required modifications in combination. The compounds that Uhlmann prepared were oligonucleotides each having a 3' phosphoryl residue. Certain of these compounds and selected unmodified oligonucleotides were assayed against HSV-1. Activity was shown only for the oligonucleotides having a 3'-phosphoryl residue (column 9, starting at line 45). It was further noted that "[c]ompared to the oligonucleotide derivatives with a 3'-hydroxyl group, known from the literature, DNA probes which comprise oligonucleotide analogs of formula I, on the one hand, offer the advantage of increased nuclease stability and, on the other, permit the acceptance of identical or different marker molecules at both ends of the oligonucleotide" (Uhlmann, column 19, starting at line 31). The importance of the 3' phosphoryl residue was therefore an important aspect of the compounds of Uhlmann. Specific teaching was not provided for oligomeric compounds without the 3' phosphoryl group, oligomeric compounds having a 5 thiophosphate group or oligomeric compounds having a phosphorus group attached to the oligomeric compound with a sulfur atom as instantly claimed.

Furthermore, Uhlmann does not provide any specific guidance or specific examples of an oligonucleotide having a 5'-terminal thiophosphate aside from the large genus of compounds described by the Markush group discussed above. In fact, in reviewing the compounds prepared by Uhlmann it is evident that the focus was the preparation of oligonucleotides having 3' phosphoryl residues, because a number of oligonucleotides were

prepared with 3' terminal phosphoryl residue but none with a 5' phosphoryl residue (Example 4).

To arrive at the instantly claimed compounds from the genus provided by Uhlmann one would have to choose specific groups for the Markush variables (R^1, $V_{terminal}$, $V_{internal}$, Q, Y, U, and W) and then further modfy the 3' position. The Examiner has failed to establish a reason to select such a compound for further modification nor a reason to modify the compounds of Uhlmann to arrive at applicants claimed oligomeric compounds and, thus fails to set forth a proper *prima facie* case of obviousness. *See e.g. Takeda*, 492 F.2d at 1360-1361, 83 USPQ2d at 1177 (addressing obviousness of required modifications steps of "ring walking" and "homologation" separately); *see, also Abbott*, 544 F.3d at 1351, 89 USPQ2d at 1170-1171 (applying principle that proper obviousness determination requires the consideration of each and every claim limitation); *In re Ochiai*, 71 F.3d 1565, 1572, 37 USPQ2d 1127, 1133 (Fed. Cir. 1995) (requiring, for purposes of 35 U.S.C. §103, a showing "that the invention as claimed in the application is obvious over cited prior art, based on the specific comparison of that prior art with claim limitations."). Indeed, the required modifications, even if taken individually, are not obvious over Uhlmann. The required modifications are even less obvious when considering the combination of limitations as a whole. Kostenko, Hamma and Sproat do not cure these defects of Uhlmann.

In addition, each of the disclosed compounds of Uhlman have a 3' phosphoryl group. There is nothing in the disclosure of Uhlman that would have provided any reason to pursue the oligomeric compounds as currently claimed. Moreover, since all of the compounds of formula I of Uhlman contain 3' phosphoryl groups, a person skilled in the art would not have had any reason to pursue the instantly recited limitation that the 3' terminus is hydroxyl or protected hydroxy.

c. Kostenko does not cure the defects of Uhlmann or provide any expectation of success

Kostenko does not cure the deficiencies of Uhlmann or provide any expectation of success with respect to the required modifications. First, Kostenko is not relevant art. Second, even if Kostenko was relevant art, it would not have provided a reason to make the

required modifications. Kostenko teaches 5'-bis-pyrenylated oligonucleotides produced by conjugating pyrene to a 5' phosphorylated oligonucleotide for the purpose of producing a fluorescent probe that can quantitatively detect hybridization. The present claims do not encompass any oligonucleotides with a 5'-phosphate group and Kostenko et al. do not teach or suggest any oligonucleotides having a 5'-thiophosphate group.

d) Hamma does not cure the defects of Uhlmann or provide any expectation of success

Hamma does not cure the deficiencies of Uhlmann or provide any expectation of success with respect to the required modifications. First, Hamma is not relevant art. Second, even if Hamma was relevant art, it would not have provided a reason to make the required modifications. Hamma teaches that producing an oligonucleotide having a 5' phosphate allows a convenient "affinity handle" for purification by strong anion exchange HPLC. The phosphate group is removed after purification to provide the final oligonucleotide. The present claims do not encompass any oligonucleotides with a 5'-phosphate group and Hamma et al. do not teach or suggest any oligonucleotides having a 5'-thiophosphate group.

i) Secondary References (Kostenko and Hamma combined)

The Examiner has acknowledged that Kostenko and Hamma teach phosphates that are attached through oxygen rather than sulfur and that neither Kostenko nor Hamma teaches or suggests 5'-thiophosphates (Final Action at page 6). The Examiner recites that "these references are relied upon to teach the advantages of the phosphate group, which are not expected to change based on how the phosphorus is attached to the oligonucleotide", and that "those in the art recognize that oxygen and sulfur are equivalent and interchangeable; as evidenced by Uhlmann et al., and appellants have presented no reasons why one would expect the possible uses for 5' phosphates would not also be applicable to 5' thiophosphates" (Final Action at page 6).

In Kostenko the 5' phosphate was further functionalized to prepare a 5'-bis-pyrenylated oligonucleotide and in Hamma the 5'-phosphate was used as an affinity handle to increase retention during strong anion exchange HPLC and subsequently removed so that the oligonucleotide could be 5' end labeled. These references disclose particular advantages of

the 5' phosphate as an intermediate group to arrive at a different 5'-substituted oligomeric compound and not advantages of an oligomeric compound having a 5' phosphate or, more importantly, a 5' thiophosphate as a the final compound. There is no motivation provided by theses references to prepare a 5' thiophosphate.

In each of Kostenko and Hamma the 5' phosphate group acts as an intermediate which is either removed or further functionalized to arrive at the final oligonucleotide of interest which does not have a 5'-phosphate group. In other words, the phosphate group is not being added to the oligomeric compound to provide a final compound for biological testing but rather is being added to provide an intermediate that is transformed to produce the final compound. The oligomeric compounds instantly claimed are useful with the 5' thiophosphate, either in pure form or for example as a composition comprising a pharmaceutically effective amount of an oligomeric compound of claim 1 and a pharmaceutically acceptable diluent or carrier as per claim 20.

The Examiner asserts that "these references are relied upon to teach the advantages of the phosphate group, which are not expected to change based on how the phosphorus is attached to the oligonucleotide", and that "those in the art recognize that oxygen and sulfur are equivalent and interchangeable; as evidenced by Uhlmann et al., and appellants have presented no reasons why one would expect the possible uses for 5' phosphates would not also be applicable to 5' thiophosphates" (Final Action at page 6). Appellants strongly disagree.

It is well known in the art that replacement of oxygen with sulfur can have a significant effect on the properties of an oligomeric compound (see for example, Antisense Research and Applications, Stanley T. Crooke and Bernard Lebleu, CRC Press, Inc., (2000), especially chapter 11 directed to phosphorothioate oligodeoxynucleotides, pages 205-221 et al., and numerous citations therein). It is well known in the art that the replacement of oxygen with sulfur can enhance properties of oligomeric compounds such as for example nuclease resistance, protein binding, RNaseH activity and translation inhibition.

e) **Sproat does not cure the defects of Uhlmann or provide any expectation of success**

Sproat teaches the synthesis of 5'-S-triphenylmethyl protected nucleoside phosphor-amidites and 5'-(S-triphenylmethyl) mercapto-oligodeoxyribonucleotides using these

phosphoramidites. The 5'-S-triphenylmethyl protected nucleoside phosphoramidites are added to the 5'-end of oligodeoxyribonucleotides which are subsequently deblocked to give a free 5'-thiol group which can be coupled to a wide variety of reagents, generating very useful probes. Sproat does not teach the use of these 5'-S-triphenylmethyl protected nucleoside phosphoramidites at any position except at the 5'-position. Sproat does not teach the preparation of a 5' thiophosphates.

The Examiner suggests that the phosphoramidite intermediates disclosed by Sproat could be used in standard synthesis protocol to produce oligonucleotides having 3'-hydroxyls (Final Action at page 4). This would not produce any of the instantly claimed oligomeric compounds as only the terminal 5'-thiophosphate has a sulfur atom attached to 5'-position. Furthermore, Sproat teaches the use of the 5'-mercapto phosphoramidite only as the last nucleoside added to an oligonucleotide so that after deprotection the thiol group can be further functionalized.

f. Mere conclusory statements of "routine modification" and "design choice" do not provide a legally sufficient reason to perform a structural modification, even after *KSR*

The Examiner asserts that based on the teachings of Kostenko and Hamma one of ordinary skill in the art recognizes that synthesis of 5' phosphate oligonucleotides is routine in the art therefore the synthesis of oligonucleotides comprising both a 5' mercapto nucleotide and a 5' phosphate is a matter of design choice made in the course of routine optimization using equivalent elements known to those of ordinary skill in the art" (Final Action starting at page 4). However, an allegation based on "design choice" and "routine optimization" does not, by itself, provide a legally sufficient "reason" to pursue a claimed limitation or structural modification, even after *KSR*.

In *Abbott*, the claims at issue recited a pharmaceutical composition for extended release of a drug. *Id.* at 1344, 89 USPQ2d at 1165. The claims recited a limitation that specified the pharmacokinetic properties provided by the extended release composition. *Id.* On the issue of validity, the challenger argued that the claims at issue were obvious because "no more than routine experimentation was needed to find a controlled release formulation that would meet the pharmacokinetic requirements stated in the [claims at issue]." *Id.* at

1347, 89 USPQ2d at 1167. In particular, the defendent urged that extended release formulations were known in the prior art and "that it would be obvious to experiment to determine which formulations were effective...." *Id.* at 1350, 89 USPQ2d at 1170. The challenger pointed out that only one month of research was required to arrive at the claimed composition. *Id.* at 1350, 89 USPQ2d at 1170. The defendent also cited *KSR*, arguing that "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." *Id.* at 1346, 89 USPQ2d at 1168.

In response, the patent holder pointed out that even if the claimed formulation resulted from the pursuit of "known options," the claimed formulation was not obvious because the "known options" in the prior art were not "finite, identified, and predictable." *Id.* at 1351, 89 USPQ2d at 1171. The District Court agreed and held that a person of ordinary skill in the art would not "have seen a benefit" in pursuing the claimed pharmacokinetic limitation. *Id.*, 544 F.3d at 1351, 89 USPQ2d at 1170. On appeal, the Federal Circuit affirmed and held that "[t]he district court appropriately applied the *KSR* standard of whether the patents in suit represented an 'identified, predictable solution' and 'anticipated success,' the words of *KSR*, to the problem of producing extended release formulations having the pharmacokinetic properties in the claims." *Id.* at 1352, 89 USPQ2d at 1172. The Court explained that "*KSR* did not create a presumption that all experimentation in fields where there is already a background of useful knowledge is 'obvious to try....'" *Id.* at 1352, 89 USPQ2d at 1171. The Court also noted that "[k]nowledge of the goal does not render its achievement obvious." *Id.*

Indeed, under *Abbott*, the determinative factor in the instant obviousness analysis is whether a person of ordinary skill in the art would "have seen a benefit" in the specifically claimed limitations. This factor turns on whether one skilled in the art has "a finite number of identified, predictable solutions." *Id.*; see also *Proctor & Gamble*, 2009 WL 1313321. The issue of whether one could have routinely performed the required modifications is inapposite. The mere *ability* of a person skilled in the art to perform a modification does not provide a *reason* to pursue that modification. This is particularly the case if one skilled in the art is faced with a large number of possible modifications. In the instant case, one skilled in the art would have, indeed, been faced with many possible modifications. For example, there

are a vast number of chemistries and configurations of those chemistries available to the art skilled for modifying oligonucleotides. The Examiner has articulated no plausible reason why one skilled in the art would select the particular chemistries used to prepare the oligomeric compounds instantly claimed from among the limitless number of possible chemistries available to the art skilled. Appellants submit that this alone defeats the Examiner's contention that the present claims are obvious. The scenario described does not represent one that involves a "finite number of identified, predictable solutions." As the Federal Circuit recently cautioned in *Proctor & Gamble*, 2009 WL 1313321, a patent is not invalid as obvious where

> researchers can only 'vary all parameters or try each of numerous possible choices until one possibly arrive[s] at a successful result, where the prior art [gives] either no indication of which parameters are critical or no direction as to which of many possible choices is likely to be successful....Similarly, patents are not barred just because it was obvious 'to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention of how to achieve it.'

Proctor & Gamble, 2009 WL 1313321 (citing *In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988)).

To arrive at the instant claims, one skilled in the art would have had to try "numerous possible choices," as the prior art does not provide any guidance for selecting and then combining the required chemistries needed to yield the claimed oligomeric compounds. All that is provided by Uhlmann, Kostenko, Hamma and Sproat are oliogmeric compounds and particular modifications that have been used in the synthesis of oligomeric compounds. However, as discussed, Uhlmann, Kostenko, Hamma and Sproat do not provide a finite number of identified, predictable solutions. Thus, one skilled in the art would not have had a legally sufficient reason to pursue any of the required modifications, even if the modifications were routine to perform.

Lastly, it is noted that the rationale of the Office Action leads to the implausible scenario that <u>all</u> oligomeric compounds would be unpatentable over combinations of references that provided directly or indirectly the chemistry modifications needed to produce them even if it meant using the references in a contradictory manner as discussed above.

B. Conclusion

For at least the reasons set forth above, Appellants respectfully submit that the Examiner erred in rejecting the subject matter of the instant claims. Appellants, therefore, earnestly request that the Examiner's rejection under 35 U.S.C. 103(a) be reversed and that the instant claims be allowed.

No fee is believed due for the submission of this paper. However, if any fees are due, the Director is authorized to charge such fees to Deposit Account No. 50-0252.

Respectfully submitted,

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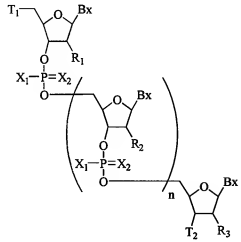
VIII. CLAIMS APPENDIX

1. (Previously presented) An oligomeric compound having the formula:



wherein:

each Bx is, independently, a heterocyclic base moiety;

T_2 is hydroxyl, or a protected hydroxyl;

T_1 is a modified phosphate having the formula:

wherein

Q is OH or CH_3

R_1, R_3 and each R_2 are, independently, hydrogen, hydroxyl, a sugar substituent group or a protected sugar substituent group;

each X_1 and X_2 is, independently, O or S wherein at least one X_1 is S; and

n is from 3 to 48.

2-3. (canceled)

4. (previously presented) The oligomeric compound of claim 1 wherein Q is CH_3.

5-10. (canceled)

11. (original) The oligomeric compound of claim 1 wherein R_1, R_3 and each R_2 is hydrogen.

12. (original) The oligomeric compound of claim 1 wherein R_1, R_3 and each R_2 is hydroxyl.

13. (previously presented) The oligomeric compound of claim 1 wherein R_1, R_3 and each R_2 are, independently, hydrogen, hydroxyl, a sugar substituent group or a protected sugar substituent group.

14. (original) The oligomeric compound of claim 1 wherein at least one of R_1, R_2 or R_3 is an optionally protected sugar substituent group.

15. (original) The oligomeric compound of claim 1 wherein each X_2 is S.

16. (original) The oligomeric compound of claim 1 wherein each heterocyclic base moiety is, independently, adenine, cytosine, 5-methylcytosine, thymine, uracil, guanine or 2-aminoadenine.

17. (original) The oligomeric compound of claim 1 wherein n is from about 8 to about 30.

18. (original) The oligomeric compound of claim 1 wherein n is from about 15 to 25.

19. (withdrawn) A method of treating an organism having a disease characterized by the undesired production of a protein comprising contacting the organism with an oligomeric compound of claim 1.

20. (previously presented) A composition comprising:

a pharmaceutically effective amount of an oligomeric compound of claim 1; and

a pharmaceutically acceptable diluent or carrier.

21. (withdrawn) A method of modifying *in vitro* a nucleic acid, comprising contacting a test solution containing RNase H and said nucleic acid with an oligomeric compound of claim 1.

22. (withdrawn) A method of concurrently enhancing hybridization and RNase H activation in a organism comprising contacting the organism with an oligomeric compound of claim 1.

23. (withdrawn) A method comprising contacting a cell with an oligomeric compound of claim 1.

24-41. (canceled)

IX. EVIDENCE APPENDIX

None.

X. RELATED PROCEEDINGS APPENDIX

None.